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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,779	KASSIS, A	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-55* is/are pending in the application.

4a) Of the above claim(s) *29,30,36-39,41-49 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-29,31-35,40 and 50-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Susan Hanley is now the examiner for this application. Her contact information can be found on the last page of this Office Action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 9, 2004 has been entered.

Claims 23-55 have been presented for examination.

Election/Restrictions

This application contains claims 29, 30, 36-39, 41-49 and 55 drawn to an invention nonelected with traverse in Paper No. November 26, 2002. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 29, 30, 36-39, 41-49 and 55 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 26, 2002.

Response to Arguments

Applicant's arguments with respect to claims 23-28, 31-35, 40 and 50-54 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

Claim 54 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The structure of claim 54 constitutes new matter because it is not envisaged by the instant application. The instant application discloses that the prodrug can have a number of prosthetic groups that include phosphate and β-D-galactosyl moieties which can be attached to quinazolinones, benzoxazoles, indoles, benzothiazoles and benzimidazoles (p. 4). The specification further discloses one specific indole prodrug specie having an indole ring that is substituted at the 3-positon of said ring by a β-D-galactosyl moiety. However, the specification does not describe any other indole prodrug species that shows to what position the prosthetic is bound to the indole ring. The disclosure that various types of rings and various kinds of prosthetic groups are connected in some manner to form prodrugs does not envisage any specific prodrug specie that specifically shows how the prosthetic group is connected to the ring specie other than those already disclosed by the specification. The specification does not support the specific prodrug specie of claim 54. Therefore, claim 54 is considered to contain new matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 23-25, 33 and 40 stand rejected under 35 U.S.C. 102(e) as being clearly anticipated by Pero et al. (US 6,538,038).

Pero et al. disclose a method of achieving targeted vascular destruction at a locality of proliferating vasculature. The method comprises administering to a warm-blooded animal a prodrug that is substantially non-cytotoxic and water soluble wherein said prodrug is converted by endogenous, extracellular phosphatase located at the site of proliferating vasculature to a water-insoluble, cytotoxic drug, as required by instant claims 23-25. The proliferating vascular disorder can be tumorogenic disorders that destroy microvessels including Kaposi's sarcoma (col. 2, lines 50-55 of the referenced patent). Pero et al. teach that their method is effective because injured microvessels exhibit a high level of phosphatase activity compared to non-injured vessels and said phosphatases are extracellular, as required by the limitations of claims 24 and 25. Pero et al. teach that the prodrug can be administered to the warm-blooded animal intravenously (col. 12, line 5), thus meeting the limitations of instant claim 33. Examples of drugs suitable for the invention are summarized by Pero et al. in Table 2 (col. 11) and column 4, lines 16-30. Therefore, the disclosure by Pero et al. meets the limitations of the indicated claims because tumors that occur in microvessels produce extracellular phosphatases at a higher level compared to normal tissue. Prodrugs having a phosphate prosthetic group, as required by instant claim 40, will be cleaved by extracellular phosphatases at the phosphatase-producing tumor site. The drugs, having lost their phosphate prosthetic, group will precipitate at the tumor cellular membrane site in their cytotoxic form.

Claims 23-28, 31-33 and 40 stand rejected under 35 U.S.C. 102(b) as being clearly anticipated by Senter et al. (EP 302,473).

Senter et al. disclose the delivery of poorly water-soluble cytotoxic drugs to tumor cells by the administration of a tumor-specific antibody-enzyme conjugate, as required in claim 23 which is drawn to a method of localizing a substantially water-insoluble drug. The disclosure also satisfies claims 25-28 and 31 because the disclosed enzyme is conjugated to a ligand which is an antibody. The antibody is responsible for binding to a tumor-specific receptor on the cell surface. Senter et al. teach that cytotoxic anti-tumor drugs tend to be poorly water soluble or water insoluble. Such drugs can be converted to prodrugs that are less cytotoxic and are water soluble (p. 6, lines 42-55). The prodrug is a substrate for the enzyme-antibody conjugate. The enzyme can be a phosphatase, which meets the limitation of claim 25 regarding the type of enzyme (p. 7, lines 33-45). Senter et al. teach that the enzyme-antibody conjugate is administered to an animal. Said conjugate binds to the extracellular surface of the target tumor cells. The prodrug is then administered and it is cleaved by the enzyme-bound antibody that is immobilized on the target cellular surface. Although Senter et al. teach do not expressly state that the cleavage of the prodrug results in a poorly water insoluble drug, the lack of water solubility of the drug the results from the enzymatic cleavage of said prodrug is an inherent property. In an example, Senter et al. disclose that Etoposide, a poorly water soluble anti-cancer agent was chemically phosphorylated to provide Etoposide-4'-phosphate, a water soluble prodrug. The phosphate group corresponds to the required prosthetic group of claim 40. Alkaline phosphatase was conjugated to an antibody called L6. The L6-phosphatase conjugate was administered to tumor-bearing mice by subcutaneous injection. The route of administration of the prodrug and the L6-phosphatase conjugate satisfies the limitations of claims 32 and 33, respectively. Control mice that also had been injected with said tumor cells received only the prodrug. The combined prodrug/L6-phosphatase therapy resulted in a significant decrease in tumor size. However, animals receiving only the prodrug experienced some decrease in tumor size as well. Senter et al. also found that whole tumor cells exhibited about ten times less alkaline phosphatase activity

compared to whole tumor cells that had been contacted with the L6-phosphatase conjugate (p. 16-18 and p. 14, last paragraph). These results demonstrate that the tumor cells produce and excrete a low amount of phosphatase (the phosphatase must be excreted by the cell since the tumors were intact) that is capable of cleaving the prodrug in the absence of the L6-phosphatase antibody. This disclosure meets the limitation of claim 23 that requires that the prodrug must be capable of being cleaved by a phosphatase that is endogenous to the tumor cell but located in the extracellular space.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23-28, 31-33, 40 and 50-53 rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan (US 5,489,525) in view of Haugland (US 5,316,906) and Hansen (US 5,851,527), Lebioda et al. (US 5,763,490), Mertens (US 5,021,220) and Christenson (US 4,107,285).

Pastan discloses monoclonal antibodies that are specific to antigens associated with prostate cells. The monoclonal antibody can be conjugated to an enzyme that is capable of converting a prodrug

that is less cytotoxic to tumor cells than the parent drug into the more active parent drug. When introduced into a host, the antibody component of the enzyme-antibody conjugate directs the conjugate to site of the prostate cells, including those at metastic sites, and binds to the prostate cells. A prodrug comprising a parent drug and a blocking group is introduced into the host. The enzyme at the tumor site converts the prodrug to the active cytotoxic drug. The advantage of this method is that the prodrug is not coupled to the antibody and the amount of drug capable of being delivered to the tumor cell site is not limited to the number of drug molecules bound to the antibody. The number of active drug molecules is amplified because the antibody-bound enzyme of the conjugate can undergo number substrate turnovers that repeatedly convert prodrug into active drug (col. 7, lines 44-68).

Pastan et al. do not disclose the employment of a phosphatase to cleave the prodrug, wherein said phosphatase is an extracellular enzyme and can cleave the prodrug. Nor does Pastan disclose employing a iodo-radiolabeld 2-phosphoryloxyphenyl-4-(3H)-quinazolinone as the substrate.

Haugland discloses precipitating substrates having a fluorescent ring bound to a blocking group that can be cleaved by a target enzyme. In particular Haugland et al. teach 2-phosphoryloxyphenyl-4-(3H)-quinazolinones (Table 6, col. 15-16 of the referenced patent) that are suitable substrates for acid phosphatases (Table 1, col. 2). The blocked fluorophores can be used in conjunction with enzyme-antibody conjugates to localize the enzyme at a particular cell site. For example, the enzyme can be linked to an antibody that is specific for a particular antigen (col. 22, lines 20-68 of the referenced patent). A phosphate group can be coupled to an antibody having an affinity for a particular cell which may be isolated or in a living animal. The enzyme-antibody conjugate can be administered to the subject. This is followed by administration of the phosphatase blocked substrate. When the blocked substrate arrives at the site of antibody-antigen binding, the phosphatase cleaves the phosphate group and the quinazolinone fluorophore, which is water insoluble, precipitates at the site of cleavage (outside the cell since the phosphatase-antibody conjugate is bound to an antigen on a cell; col. 23 of the referenced patent).

Lebioda et al. disclose that prostatic acid phosphatase (PAP) is produced by the prostate gland and found in relatively high concentrations in seminal fluid. In a healthy subject, PAP is contained in the reproductive organs. However, as prostate cancer develops, the cancel cells spread throughout the body and secrete large quantities of PAP (col. 1, lines 50-68 of the referenced patent).

Hansen teaches the administration of antibody-enzyme complexes that are target for a particular site in the body and a separate soluble substrate-agent conjugate comprising at least one therapeutic or diagnostic agent and a prosthetic group. The enzyme catalyzes the conversion of the soluble substrate agent to produce a less soluble agent that is deposited at the target site (col. 3-4 of the referenced patent). The agent can be therapeutic or diagnostic and can comprise radioisotopes or chromophores. The therapy is suitable for treatment of tumors. A radioactive agent can comprise a radionulcide such as I-123, I-125 or I-131 and can function with chromophores or fluorophores in the agent (col. 11, lines 38-51 of the referenced patent).

Mertens et al. disclose that radioiodinated compounds can be prepared from halogenated heteroaromatic compounds. The heteroaromatic substrate can have a pyridine, quinoline or indole nucleus (col. 3, lines 5-20 of the referenced patent).

Christenson discloses that quinazolinones can be easily converted to radiolabeled derivatives (col. 3, lines 35-50 of the referenced patent).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ an iodo-radiolabled 2-phosphoryloxyphenyl-4-(3H)-quinazolinone as a substrate for an acid-phosphatase conjugated to an antibody that is specific for prostate tumor cells in order carry out the method disclosed by Pastan. An acid-phosphatase could be targeted for prostatic tumor cells by conjugating it to an antibody that is specific for an antigen on a prostate tumor cell in the method of Pastan. Thus, according to the method disclosed by Pastan, an iodo-radiolabled 2-phosphoryloxyphenyl-4-(3H)-quinazolinone would serve as a prodrug that, after administration to a host, would be cleaved by the acid phosphatase-antibody that is bound to the tumor cell. After cleavage of the phosphate group, the

water-insoluble iodo-radiolabled 2-oxyphenyl-4-(3H)-quinazolinone would precipitate at the target site on the surface of the prostate cell. The ordinary artisan would have known would have been motivated to use a phosphatase-conjugated antibody and a phosphorylated quinazolinone in his targeting method because Haugland demonstrate that that antibody-phosphatase conjugates were well known for binding to target sites on cells and that phosphorylated quinazolinones could be cleaved by phosphatases leaving a precipitated fluorescent quinazolinone at the site of cleavage on the outside of the cell. The ordinary artisan would have been further motivated to make a radio-labeled iodinated 2-phosphoryloxyphenyl-4-(3H)- quinazolinone because Hansen demonstrated that such substrates which are water soluble until they are cleaved by a target enzyme are suitable for depositing radioactive substances at tumor site for cancer therapy. This would have been desirable for the treatment of prostate cancer. The ordinary artisan would have known from Mertens et al. and Christenson that it was well within the purview of the ordinary artisan to make iodo-radiolabled quinazolinones from halogenated substrates. Lebioda et al. was cited to demonstrate that prostatic acid phosphatase is an extracellular enzyme which could cleave the phosphoryl-blocked 2-phosphoryloxyphenyl-4-(3H)-quinazolinone taught by Haugland.

Claims 23-28, 31-33, 40 and 54 rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan (US 5,489,525) in view of Haugland (1995), Haugland (US 5,316,906) and Hansen (US 5,851,527), Lebioda et al. (US 5,763,490), Mertens (US 5,021,220) and Rose (US 5,816,259).

The disclosures of Panstan, Haugland (US 5,316,906), Lebioda et al. and Mertens is discussed *supra.*

Pastan et al. does not disclose the employment of a phosphatase to cleave the prodrug, wherein said phosphatase is an extracellular enzyme and can cleave the prodrug. Nor does Pastan disclose employing a iodo-radiolabeld 3-indolyl phosphate as the substrate.

Haugland (1995) teaches 6-chloro-3-indolyl phosphate as a blocked substrate that will precipitate at an extracellular site when cleaved by a phosphatase-antibody bound to a cell (p. 220 and 224).

Rose discloses that halogenated indole phosphate can be converted to a radio-iodolabled indole phosphate that can be cleaved at target cells to deposit the radio-labeled indole at the cell (Fig. 17 and col. 10, lines 60-68 through col. 11 of the referenced patent).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ an radio-iodolabled indole-3-phosphate as a substrate for an acid-phosphatase conjugated to an antibody which is specific for prostate tumor cells in order carry out the method disclosed by Pastan. An acid-phosphatase could be targeted for prostatic tumor cells by conjugating it to an antibody that is specific for an antigen on a prostate tumor cell. Thus, according to the method disclosed by Pastan, an radio-iodolabled indole-3-phosphate would serve as a prodrug that, after administration to a host, would be cleaved by the acid phosphatase-antibody that is bound to the tumor cell. After cleavage of the phosphate group, the water-insoluble radio-iodolabled indole would precipitate at the target site on the surface of the prostate cell. The ordinary artisan would have known would have been motivated to use a phosphatase-conjugated antibody and a phosphorylated indole in the targeting method of Pastan because Haugland demonstrate that that antibody-phosphatase conjugates were well known for binding to target sites on cells and that phosphorylated indoles could be cleaved by phosphatases leaving a precipitated fluorescent indole at the site of cleavage on the outside of the cell. The ordinary artisan would have been further motivated to make a radio-iodolabled indole-3-phosphate because Hansen demonstrated that such substrates, which are water soluble until they are cleaved by a target enzyme, are suitable for depositing radioactive substances at tumor site for cancer therapy. This would have been desirable for the treatment of prostate cancer. The ordinary artisan would have known from Rose and Christenson that it was well within the purview of the ordinary artisan to make iodo-radiolabled indoles from halogenated substrates. Lebioda et al. was cited to demonstrate that prostatic acid phosphatase is an extracellular enzyme which could cleave the radio-iodolabled indole-3-phosphate taught by Haugland.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JEAN C. WITZ
PRIMARY EXAMINER